

well into the rectum, the introduction of an electrode well up into the rectum often produces much local distress, to which the physician all too often pays not the slightest note, having previously made up his mind that it possessed great therapeutic merit and should be employed regardless of the fact that oftentimes it is severe punishment to the patient and tends rather to retard than to hasten a cure. Even the hot water thermaphore often causes great discomfort in cases where the bulging prostate is much pressed upon. Manipulation of, and pressure on, an acutely inflamed prostate is just as illogical as squeezing or pressure on a tonsil in a patient with acute follicular tonsillitis, and in practice a really intelligent patient resents any kind of pressure or manipulation on an acutely inflamed prostate. All these electrodes are almost certain to do just that.

With chronic conditions heat locally applied may be of considerable value; but, after all, it is only one factor in the therapeutic management. Certainly no one has brought forth any worth while evidence that the beneficial effects of heat in this area is the result of any bactericidal action of heat. Obviously such notions are only the result of wishful thinking. While the beneficial effects are undoubted, this is effected in all probability through hyperemia, the hastening of absorption of exudate, promotion of drainage through the ducts, both by reason of the hyperemia and the pressure of the electrode on the prostate.

My more limited clinical experience tends to exactly bear out Doctor Herring's conclusion as to the comparative efficiency of the several types of machines. Doctor Herring, in passing, refers to the criterion of cure. I should like to emphasize that such criteria should always be based on every fact relative to a given case, including subjective symptoms, physical findings and laboratory data.

Finally, the local application of heat to the prostatic area is only one of the various agents of proven value in the treatment of inflammations and infections of the prostate and seminal vesicles. The great criticism, concerning many types of physiotherapy, is that their advocates too often manifest an altogether too exaggerated notion of their efficiency, to the neglect of other proven and recognized forms of therapy. Heat at best, no matter how applied, is only an adjuvant, not a cure-all. If we recognize its limitations as well as its great value, and prescribe it intelligently without expecting miraculous results to follow in every case, and at the same time display judgment in the selection of machines, such as Doctor Herring has done, we may give much satisfaction to our patients and ourselves by its employment.

A Final Warning.—Only in the occasional case which fails to respond to more moderate measures, should we resort to ultravigorous massage or an extreme degree of heat to the region of the prostate. Otherwise, there will be many flare-ups resulting in subacute prostatitis and even epididymitis, sometimes becoming quite acute. Clinically such observations are not infrequent. One should resist a certain human tendency to argue that if a little is good, more is better!

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DOCTOR HERRING (closing).—We are in full accord with Doctor Epstein's statement that the mechanism of producing therapeutic results in artificial fever is not known. Recent work, however, more and more is tending to prove that it is the heat alone that produces the therapeutic results, and not some vague unknown secondary factor. Based on this conclusion, I have been applying heat in known amounts to local parts.

I appreciate Doctor Day's appraisal of the work as outlined in my paper. I agree with him that acute conditions of the prostate should not be handled by rough massage and unknown quantities of heat. It was because of this fact that I designed an electrode shaped and water-cooled to minimize traumatization, and have recorded temperatures so that no haphazard procedure need be employed to an organ so susceptible to violent adverse reactions. Under these controlled conditions I have had no complications, and have not hesitated to treat a prostate with heat, in the face of most acute infections. However, I should say here that in the acute stages of gonorrhea, I do not use this method.

CLINICAL STUDIES WITH PROTAMINE-INSULIN

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INTRODUCTION.—A large amount of investigative study in the last ten years has been directed to the problem of slowing the rate of insulin absorption after injection into the subcutaneous tissues. This work has been stimulated by the difficulties found in maintaining a satisfactory control in many diabetic children, and in diabetic adults of the more severe forms, where blood sugar values may range in twenty-four hours from a dangerously low figure to an extreme hyperglycemia. The first evidence of possible success in solving this problem was in the reports from the Steno Memorial Hospital of Copenhagen¹ on the studies with protamine-insulinate, and the later publications from the same institution² and from the George F. Baker Clinic of Boston.³

PROTAMIN BUFFER: METHOD OF HAGEDORN OF COPENHAGEN

Early in this year the Eli Lilly Company began supplying a preparation of iletin with protamine buffer, using in preparation the methods of Doctor Hagedorn of Copenhagen. This protamine-insulin is distributed for clinical studies with the same generosity, and in the same spirit, as was shown by this company in 1922 with insulin. This report is concerned with clinical observations on twenty-five diabetic patients who have been using the Eli Lilly protamine-insulin for sufficient time to justify some conclusions as to the early effects. The results of similar studies have recently been published by Dr. R. M. Wilder,⁴ of the Mayo Clinic, Dr. E. P. Joslin,⁵ and Kerr, Best, Campbell and Fletcher⁶ of Toronto.

REPORT OF CASES

CASES 1 and 2.—The first patients selected for the studies now presented were two children, twin sisters, with the onset of diabetes in January and October, 1931. Both have been under observation in this clinic since diabetes was found. Both have been frequently hospitalized in the five years for acute complications. One had eleven admissions in five years and the other thirteen. Both had been taking diets of the same values, for a number of months before this study was begun, with insulin given four times in each twenty-four hours. These patients were held in the hospital for three months, with daily urine analyses and frequent blood sugar studies. Table 1 gives some of the significant results of urine analyses for the collection periods. In this table the designated day indicates the interval following change in dosage of regular insulin (R-I) or of protamine-insulin (P-I).*

Chart 1 shows a comparison of the blood sugar curves with regular insulin and with protamine-insulin. Curve 2 was obtained soon after an acute head cold, and before the morning dose of protamin insulin had been reduced to 20 units. The sister of this patient has had a record so similar as to make any detailed report almost a duplication.

Acute complications and breaking diets can cause sharp loss of diabetic control in both patients, but the even control possible with the protamine-insulin gives greater possibilities for increased resistance to infections and better possi-

* For convenience, regular insulin in this report is designated as R-I, and protamine-insulin as P-I.

TABLE 1.—*Glycosuria. Child*

Age 8½ years			Diet: C. 150, P. 60, F. 60				Insulin: 14-4-8-6			
Time:	7:00 A. M.-N.		N.-7:00 P. M.		7:00 P. M.-M.		M.-7:00 A. M.			
	Vol.	Gms.	Vol.	Gms.	Vol.	Gms.	Vol.	Gms.	Dosage	
Day										
	650	3.9	550	tr.	650	4.2	240	6.8	R-I 14-4-8-6	
1	400	16.0	550	7.7	650	7.2	350	5.8	R-I 14-4-0-0	
2	650	25.4	250	6.2	720	25.8	180	8.4	P-I 14 at	
4	400	0.	275	4.7	110	0.	400	10.0	3:30 P. M.	
1	550	3.8	150	0.7	450	2.7	550	18.1	R-I unchanged	
4	500	tr.	300	0.	150	3.3	200	4.6	P-I at 4:30	
1	1,000	37.0	600	24.0	150	1.5	200	1.0	P-I at 6 P. M.	
8	550	18.1	650	3.9	350	tr.	250	7.0		
1	600	3.0	600	11.4	400	5.6	No specimen		R-I stopped	
3	200	3.6	500	tr.	310	2.4	300	0.	P-I 20 at	
75	280	0.	200	0.	280	0.	340	0.	6 A. M. 16 at	
									5 P. M.	

bilities for normal development than could be secured with such blood sugar curve as seen in 1 of the chart. In the summary of urine analyses of Table 1, protamine-insulin given at 3:30 p. m. does not give as satisfactory control of glycosuria as does the 4:30 time. The same is true when the protamine-insulin was given at 6 p. m. When all regular insulin was stopped and protamine-insulin was given twice daily, there appeared definite increase in glycosuria and urine volumes when the interval between morning and evening doses was changed. The best control was manifest when injections were given from eleven to twelve hours apart. When this interval between injections was observed, the meal times for breakfast and supper were changed, and no increase in glycosuria occurred when protamine-insulin was given before, with or after the morning and evening meals. In all other patients who have been taking the protamine-insulin it has been routinely advised to fix a definite time for the injections with a twelve-hour interval, with the morning and evening meals within an hour before or after taking the insulin.

ON DISTURBED CONTROL

Table 1 also indicates the disturbed control that frequently follows the change from regular insulin to protamine-insulin and the increased glycosuria that may persist from two to ten days after even slight changes in the time of protamine-insulin injections. This sensitiveness appears to be much more pronounced in those patients who have been using regular insulin for some time than in new or mild diabetic patients who have never taken insulin. It is possible that a glycogenic function that has become somewhat adjusted to the more acute effect of regular insulin may be slower in adaptation to the more gradual effect of the protamine preparation.

REPORT OF CASES

CASE 3.—Chart 2 shows blood sugar curves in an adult patient at the beginning and the end of a hospital study of three weeks. The tolerance gain is marked for this short time, especially when it is known that the patient entered the hospital before full recovery from an acute ketosis. Diabetes was of seven years' duration and control has always been very irregular. Full control is main-

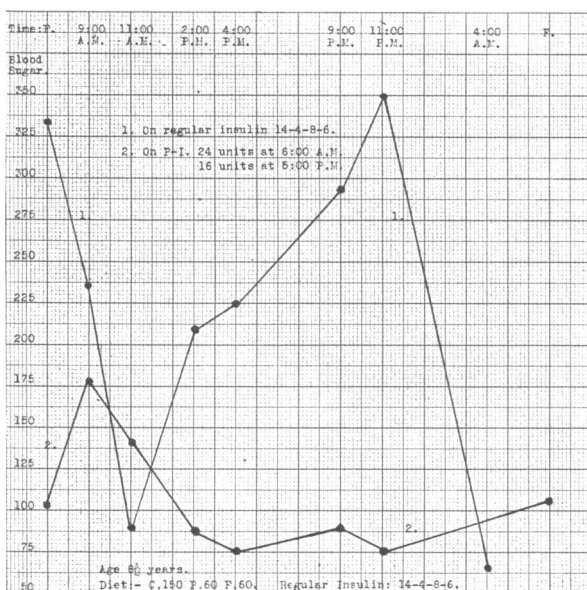


Chart 1

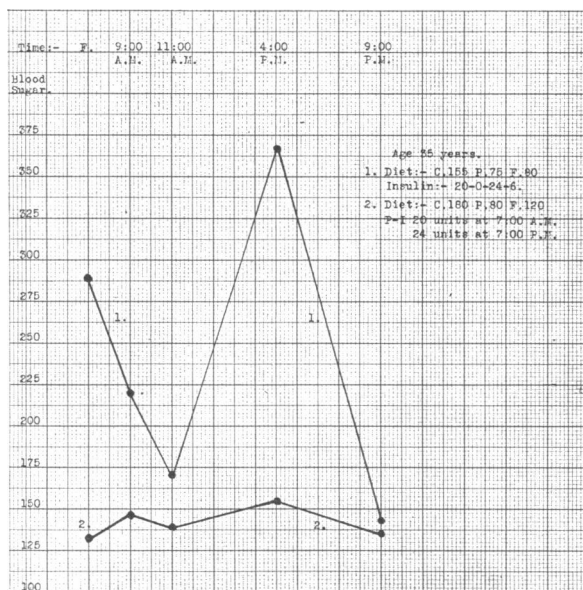


Chart 2

TABLE 2.—*Glycosuria. Adult*

Time: 7 A. M.-7 P. M.		7 P. M.-7 A. M.		Dosage
Day	Vol.	Gms.	Vol.	
	1,825	32.8	1,100	Diet: C. 155, P. 75, F. 80 R-I 20-0-24-6.
1	3,100	122.0	1,000	R-I 20-0-0-0.
2	850	60.3	650	P-I 24 at 6 P. M.
3	1,300	7.8	1,200	
4	1,200	6.0	1,650	
7	1,400	0.	1,300	
1	1,400	7.0	1,500	R-I stopped.
2	1,400	0.	1,300	P-I 22 at 7 A. M.
3	1,600	0.	1,300	24 at 7 P. M.
5	1,450	0.	1,160	Diet: G. 180, P. 80, F. 120
8	1,340	0.	1,020	
10	1,300	0.	500	P-I 20 units 7 A. M. 24 units 7 P. M. Leaves hospital

tained since this patient left the hospital. Table 2 again shows the increase in glycosuria that immediately follows any change in insulin, either in unit dosage or time.

The clearing of marked periodic fatigue and improved endurance in the ten days since discharge from the hospital are mentioned by the patient as marked change in symptoms. There is evident improvement in nervous stability and this is probably due to the more evenly maintained blood sugar.

Seven patients with some cardiovascular complication are included in this group. In all of these the cardiovascular condition developed from one to fifteen years after the onset of diabetes. The ages of the seven patients range from 52 to 75 years. All have required insulin for several years, and diabetic control has been impossible even when insulin was given from three to six times daily.

ON INCREASE OF GLYCOSURIA WITH INSULIN CHANGE

An increase in glycosuria with each insulin change is seen in Table 3. This appears to clear as gradually in a patient of seventy-two years as in a patient of eight and one-half years. The afternoon dose of protamine-insulin was taken after the evening meal during the time this patient was in the hospital, which is the time covered by the data of Table 3.

COMMENT ON PATIENT GROUPS

Three patients of the seven with cardiovascular complications were able to hold full diabetic con-

trol on one dose of protamine-insulin, when regular insulin had been taken in two to four doses previously. Loss of early morning or late afternoon fatigue, increased general strength and clearer vision are symptoms most frequently given by this small group after the change from regular insulin to protamine-insulin. Some reason for this is seen in the blood sugar values as follows:

Age 70. Diabetes since 1932. Angina since 1935.
Diet: C. 150, P. 60, F. 100.

After one month on protamine-insulin with dosage sixteen units morning and twelve units afternoon. Former regular insulin, 20-6-12-8.

Blood Sugars Fasting 9 a. m. 11 a. m. 5 p. m.
175 188 172 168

One patient who went to work after school was out in June had to change his routine of meals and protamine-insulin injection time. Working from 3 p. m. to midnight required him to have breakfast late each morning and supper at 1 a. m., after returning from work. He had been taking protamine-insulin twice daily and had held a fairly even diabetic control when attending school. Night-frequency returned and also high blood sugar values with glycosuria of high percentage. By taking regular insulin at 1 a. m. and protamine-insulin at 9:30 a. m. before breakfast, he has been

TABLE 3.—*Glycosuria. Cardiac*

Diet: C. 150, P. 60, F. 120

Time: 7 A. M.-7 P. M.		7 P. M.-7 A. M.		Dosage
Day	Vol.	Gms.	Vol.	
	860	13.7	1,300	R-I 18-0-14-4.
1	600	0.	1,200	R-I 18 -0-0-0.
2	1,300	9.8	1,200	P-I 18 at 6:30 P. M.
1	900	18.0	1,150	R-I stopped.
3	750	16.5	850	P-I 20 units A. M. and P. M.
5	500	2.5	1,000	Time 6:30.
6	400	0.	800	
1	400	0.	850	P-I 24 Units A. M.
4	800	0.	750	16 units P. M.
8	820	0.	760	

Age 72 years. Onset of diabetes June, 1926. Began insulin in February, 1928. Chronic myocarditis. Sclerotic aortitis. First cardiac symptoms, 1934.

able to maintain satisfactory control and continue at work. This patient had night polyuria that lasted for about twelve hours after he first began taking protamine-insulin. Another patient, age twenty-four years, had a sharp ketosis immediately following the first dose of protamine-insulin. This cleared completely in about fourteen hours without any additional insulin. Three other patients have had acute diabetic symptoms for twelve to thirty-six hours after the first injection of protamine-insulin, and all have lost these symptoms without increasing the unit dose of protamine-insulin or taking regular insulin. Two patients had symptoms of hypoglycemia following the first evening injection of protamine-insulin. With one patient the symptoms began about 4 a. m., several hours before the injection of regular insulin was due. The second patient experienced hypoglycemic symptoms two hours after breakfast. These were evidently influenced by the morning dose of regular insulin. These symptoms continued more or less severe until about 9 p. m. even with extra carbohydrate taken during the day to at least 80 grams.

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Eight patients were never able to come under satisfactory control with plain protamine-insulin during several weeks of close observation. Blood sugars were maintained at a more even level, but held values of 200 to 300 milligrams, with high percentage of glycosuria. Since protamine-insulin in combination with either zinc or calcium has been available, these patients have responded with more satisfactory control. The studies of Scott and Fisher⁷ on the effects of giving diabetic dogs protamine-insulin combined with small amounts of zinc, and the experimental and clinical studies reported by Kerr⁸ indicate a longer insulin effect with zinc than was found with protamine-insulin alone. During the short time that the Lilly preparations, that combine either zinc or calcium with protamine-insulin, have been available, there has been an increasing amount of evidence that these combinations give insulin effects of longer duration than has been found with plain protamine-insulin solutions, with less diabetic disturbance at the beginning of the treatment or with any change either in unit dosage or in time of injection. Which of the two preparations, zinc or calcium, is the more stable and will give the longer insulin yield is now being studied. The blood sugar curve of Table 2 gives evidence of the degree of diabetic control possible with calcium protamine-insulin.

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But two patients of the twenty-five here reported have continued to take regular insulin for one period of the day. One takes this for the morning insulin and the other for the late night dose. Several patients of this group studied had to change back to the regular insulin for several days. This shift was made without disturbance, and the later change back to protamine-insulin caused none of the evidence of loss of diabetic control that appeared earlier.

IN CONCLUSION

1. Those diabetic patients who have used regular insulin for some time before beginning protamine-insulin often show an acute diabetic disturbance that may last from three to five days. Loss of control to some degree may immediately follow any slight change in unit dose, or in time of protamine-insulin injection. Failure to secure satisfactory control with the new insulin may result from frequent changes in time of injection or in unit dose.

2. In the group of patients now reported, it was found that the protamine-insulin had a unit value somewhat less than U-40. Usually four to eight units more were required with the protamine-insulin solution. Since the zinc and the calcium combinations have been used there is evidence that these are more nearly the same in unit value as regular insulin of U-40 strength.

3. Observations indicate that an interval between protamine-insulin injections of twelve hours gives satisfactory results, rather than giving the dose in relation to meals.

4. Change from protamine-insulin to regular insulin and back again to the protamine can be done without serious disturbance in control.

5. All patients have expressed a feeling of increased endurance and relief of periodic fatigue soon after beginning protamine-insulin, even before satisfactory control is obtained.

6. Hypoglycemia may be difficult to correct because of the continued absorption of insulin, and may appear at the beginning of the change to protamine-insulin, when regular insulin is taken at one or more periods. Subnormal values for blood sugar may be found without definite symptoms. This may require more frequent blood sugar tests, especially in patients with some cardiovascular complication. The more even blood sugar control should give greater safety for these patients in that there should not be the rapid drop in blood sugar that was occasionally found with regular insulin.

7. Patients using protamine-insulin should be warned of the necessity of keeping the preparation in the icebox after mixing, and to shake the bottle before each withdrawal of dose.

8. The combinations of insulin with protamine buffer, together with either zinc or calcium, give a more even blood sugar control throughout the full twenty-four hours than has been possible with regular insulin alone in the severe diabetic. Clinical observations for longer time will give the full picture of value for these new preparations, but the controls secured in the months they have been used offer great hope for the future.

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A NEW APPROACH TO RESECTION OF CANCER OF THE COLONIC FLEXURES*

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DISCUSSION by H. Glenn Bell, M.D., San Francisco; Mark Lewis Emerson, M.D., Oakland; Harold Brunn, M.D., San Francisco; John B. deC. M. Saunders, F.R.C.S., San Francisco.

CARCINOMA involving the splenic and hepatic flexures has too frequently been regarded as inoperable because of the difficulties of resection and the high mortality occasioned by the removal of this portion of the bowel. For this reason many palliative operations have been done. Permanent colostomies are necessary at times, but they have many objectionable features, and should be avoided if reestablishment of the continuity of the bowel is at all possible without too great a risk.

DIFFICULTIES AND DANGERS OF RESECTION

The difficulties and dangers of resection have been caused largely by the poor exposure through the usual anterior route, making the operation long and subjecting the patient to shock; in addition, the flexures are fixed and inaccessible, the blood supply comes from the posterior wall still farther from the incision, and it is often impossible to remove completely the glandular metastases in the surrounding tissues. If the patient survive the immediate operation, too frequently he is left with a permanent colostomy or fistula, and eventually dies of infection or a recurrence of the disease.

Some of our surgeons argue that a permanent colostomy can be made so inoffensive that it is not objectionable. It is always, however, a source of great care, gives an unmistakable odor however perfectly it may function, and leaves the patient with a physical handicap and mental distress.

We do not hesitate to resect a cancer of the stomach even in the presence of known metastases in the liver, and in spite of a fairly high mortality rate, because, without resection, patients with this lesion lead a miserable existence; on the other hand, if resection is successful they may live fairly comfortably for from one to five years. In my opinion we should adopt a similar attitude toward cancer of the colon.

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The transverse incisions through the rectus muscle or the combined rectus and costal incisions have never become popular as a method of opening the abdomen, because of the time consumed in closure and because the wall is weakened in a high percentage of cases due to interference with the nerve supply, or infection. The lumbar incision of Koster,¹ "extending from the tip of the twelfth rib to the anterior-superior spine," approaches the mesenteric vessels from the retro-peritoneal space, and gives a fairly good approach to the blood supply but does not give adequate exposure for a rapid and complete excision.

INCISION USED BY THE AUTHOR

I have been using a pericostal-transabdominal incision which parallels the twelfth rib and extends from the lumbar fascia in the back to the sheath of the rectus abdominis muscle in front, at the level of the umbilicus—a modification of the usual incision for exposure of the kidney. Instead of curving downward toward the groin, the incision curves upward around the tip of the twelfth rib, extends to and nicks the sheath of the rectus muscle, but does not transect the muscle itself. If it interferes with the innervation of the musculature at all it is only to a slight degree.

It would seem that this incision should violate every principle of good surgery by dividing both muscle fibers and their nerve supply, which would make herniation inevitable. This, however, is not the case. The recent work of Coyte,¹ and Davies, Gladstone and Stibbe,² has shown that the eleventh intercostal nerve does not course directly across the abdomen, as our anatomies have taught us, but first loops downward before entering the rectus muscle just above the umbilicus, and then again turns downward within its fibers. The lower dorsal nerve (subcostal or twelfth nerve) does not follow the twelfth rib, but comes out much lower and nearer the spine, with the ilio-inguinal and iliohypogastric nerves, and after looping downward, enters the rectus muscle below the umbilicus and courses downward. This incision is made between and parallel to the eleventh and twelfth nerves, which explains the lack of injury to the nerves and lack of degeneration of the muscles which we have found in actual practice. It may be of interest that this incision was developed and used successfully before the true anatomic arrangement—which explains its anatomic soundness—was suspected.

Formerly we were taught that each segment of the rectus muscle was innervated by a single nerve, and that severance of that nerve would result in atrophy of the corresponding segment. In actual practice, however, this complication was seldom seen. An explanation of this fact is offered in the work of Davies, Gladstone and Stibbe,² who stated, in a recent article: "Moreover, any one nerve at the lateral border of the rectus is distributed to two segments of muscle. It is certain, therefore, that the rectus segments do not receive a segmental nerve supply, but that each segment is supplied by three segmental nerves at least." Goinard³ also suggested that the nerve